REMARKS/ARGUMENTS

The Present Invention

The present invention is directed to a method of preparing autologous T-lymphocytes for re-introduction into a patient having cancer and a method of treating a patient having cancer.

The Pending Claims

Claims 1-13, 15, and 16 are pending of which claims 15 and 16 are withdrawn.

The Final Office Action

The final Office Action rejects claim 4 under 35 USC Section 112, first paragraph, as allegedly containing new matter. Claim 4 is also rejected under 35 USC Section 112, second paragraph, as allegedly indefinite. The rejection of claims 1 and 14 under Section 102 (e) in view of U.S. Patent 5,874,556 (hereinafter the '556 patent) is maintained by the final Office Action. The rejection of claims 1-3 and 5-10 under Section 103 (a) in view of the '556 patent in view of U.S. Patent 6,562,347 (hereinafter the '347 patent), is maintained. Claims 1-3 remain rejected under Section 103 (a) in view of the '556 patent in view of Wang et al., *Exp. Opin. Biol. Ther.* 1: 277-290 (2001) (hereinafter Wang et al.). Claims 1 and 11 remain rejected under Section 103 (a) in view of the '556 patent in view of U.S. Patent 6,312,957 (hereinafter the '957 patent). Claims 1, 12, and 13 remain rejected under Section 103 (a) in view of the '556 patent in view of Roifman et al., *Pediatric Research* 48: 6-11 (2000) (hereinafter Roifman et al.). Claims 1, 12, and 13 remain rejected under Section 103 (a) in view of the '556 patent in view of Hattori et al., *J. Immunology* 144: 3809-3815 (1990) (hereinafter Hattori et al.). Claims 1, 12, and 13 remain rejected under Section 103 (a) in view of the '556 patent in view of Asami et al., *Eur. J. Haematology* 57: 278-285 (1996) (hereinafter Asami et al.). Reconsideration of the rejections is hereby requested.

Amendments to the Specification and Claims

The specification at paragraph [0011], line 9, has been amended to recite "the 209-2M peptide (SEQ ID NO: 5)." As discussed in the previous Reply submitted on August 29, 2007, SEQ ID NO: 5, which is the amino acid sequence IMDQVPFSV, is incorporated into the

specification of the instant application by reference to Liu et al., *J. Immunology* 167: 6356-6365 (2001) (hereinafter Liu et al.).

Claims 14 and 17-32 have been canceled. No new matter has been added by way of the amendments.

Discussion of the Non-Elected Claims

The final Office Action contends that a complete reply to the final Office Action must include cancelation of the non-elected claims. While claims 17-32 have been canceled herein, claims 15 and 16 remain pending but withdrawn, because claims 16 and 17 depend from claim 1 and are accordingly eligible for rejoinder. MPEP 821.04 Thus, the cancellation of claims 16 and 17 is not required.

Discussion of the New Matter Rejection

Claim 4 is rejected as allegedly containing new matter. Specifically, the Office Action contends that the recitation of "the 209-2M peptide (SEQ ID NO: 5)" is new matter. The rejection is traversed for the reasons set forth below.

The recitation of "209-2M peptide" is found in the specification at, for example, paragraph [0011], line 9, paragraph [0026], line 1, paragraph [0027], line 4, and in original claim 4. Thus, this part of the rejected phrase is not new matter.

As stated in the previous Reply submitted August 29, 2007, the amino acid sequence of the 209-2M peptide, namely IMDQVPFSV, is incorporated by reference to Liu et al., *J. Immunol.* 167: 6356-6365 (2001); hereinafter Liu et al. Liu et al. teaches IMDQVPFSV as the amino acid sequence of the 209-2M peptide in the first sentence of the second complete paragraph of the left column on page 6357. Replacing the identified material incorporated by reference with the actual text is not new matter. MPEP 2163.07 (b).

The final Office Action contends that Liu et al. is *not* incorporated by reference into the instant application. On the contrary, the specification at paragraph [0062] states that all references cited in the application are entirely incorporated by reference. Liu et al. is cited in the application at, for instance, paragraph [0013], lines 6 and 7. Accordingly, the entire

contents of Liu et al., including the teaching of the amino acid sequence of the 209-2M peptide, is, in fact, incorporated by reference.

Furthermore, attached hereto is a Statement Under 37 CFR 1.57 (f), stating that the amendment to the specification, as presented herein, and the amendment to the specification and claim 4, as presented in the Reply to Office Action submitted on August 29, 2007, represents material previously incorporated by reference. Accordingly, the amendments do not contain new matter.

In view of the foregoing, claim 4 does not contain new matter. Applicants therefore request the withdrawal of the rejection.

Discussion of the Indefiniteness Rejection

Claim 4 is rejected as allegedly indefinite for the recitation of "the 209-2M peptide (SEQ ID NO: 5)." Specifically, the Office Action alleges that the rejected phrase is vague, since Liu et al. teaches that the amino acid sequence of the 209-2M peptide is IMDQVPFSV, whereas Kammula et al., *J. Immunol.* 163: 6867-6875 (1999) (hereinafter Kammula et al.) teaches that the sequence is IMQVPFSV. The rejection is traversed for the reasons set forth below.

The recitation of "the 209-2M peptide (SEQ ID NO: 5)" finds antecedent basis in the specification at paragraph [0011], line 9, as amended herein. One of ordinary skill in the art reading the instant application recognizes that the meaning of "the 209-2M peptide (SEQ ID NO: 5)" is a peptide which has the amino acid sequence of SEQ ID NO: 5 of the Sequence Listing. The amino acid sequence of SEQ ID NO: 5, namely, IMDQVPFSV, is properly incorporated by reference to Liu et al., as discussed herein. Therefore, the meaning of "the 209-2M peptide (SEQ ID NO: 5)" in the context of the claim and of the instant specification is clear and definite to one of ordinary skill in the art.

The originally-filed specification also teaches at paragraph [0011], line 9, that the 209-2M peptide is amino acids 209-217 of gp100 with a methionine substitution at position 210. The amino acid sequence of gp100 at the time of filing the instant application was well-known in the art. See, for example, Kawakami et al., *Proc. Natl. Acad. Sci. U.S.A.* 91: 6457-

6462 (1994); a copy of which is attached hereto. Therefore, the rejected phrase was clear to one of ordinary skill in the art at the time of filing the instant application.

Furthermore, as stated in the Declaration of Dr. Udai Kammula, the sequence of the 209-2M peptide as published in Kammula et al. contained a typographical error and that the true sequence of this peptide is IMDQVPFSV. Moreover, according to the Declaration of Dr. Udai Kammula, one would recognize that the amino acid sequence of the 209-2M peptide reported in Kammula et al. contained a typographical error, since it was recognized that the 209-2M peptide is amino acids 209-217 of gp100 with an amino acid substitution of methionine at position 210 (Footnote 2 on page 6867 of Kammula et al.) and one recognized that the amino acid sequence of amino acids 209-217 of gp100 was ITDQVPFSV (Kawakami et al., *Proc. Natl. Acad. Sci. U.S.A.* 91:6458-6462 (1994)).

In view of the foregoing, the metes and bounds of claim 4 can be ascertained by the ordinarily skilled artisan. Applicants therefore request that the rejection is withdrawn.

Discussion of the Anticipation Rejection

The rejection of claims 1 and 14 as allegedly anticipated by the '556 patent is maintained by the final Office Action. As a first matter, claim 14 has been canceled herein. Thus, the rejection as it pertains to this claim is moot. The rejection as it pertains to claim 1 is traversed for the reasons set forth below.

The final Office Action maintains that each and every limitation of claims 1 and 14 are taught by the '556 patent. Specifically, the final Office Action contends that the '556 patent teaches (i) obtaining PMBCs from a patient immunized with an antigen of the cancer of a patient, since the '556 patent teaches that cytotoxic T cells (CTLs) specific to a particular type of tumor can be isolated and administered to a patient having a tumor with the effect that the CTLs ameliorate the tumor. The '556 patent also allegedly teaches (i) of claim 1, as it teaches that T cells with apparent tumor specificity can be isolated from human tumors and that such human tumor infiltrating lymphocytes (TILs) have been expanded in vitro and used to treat cancer patients. See, column 2, lines 7-19. The final Office Action contends that a human patient having a human tumor is considered as a patient immunized with an antigen of cancer.

The final Office Action contends that the '556 patent teaches (ii) stimulating the PBMCs with the antigen of the cancer in vitro, when the '556 patent teaches that the combination of antigen and IL-2 causes proliferation of primary CD8+ T cells in vitro.

Furthermore, the final Office Action contends that the '556 patent teaches a retroviral vector that lacks an exogenously introduced gene that enables phenotypic selection, since the '556 patent teaches that a vector comprising the IL-2 gene, which "preferably" comprises a phenotypic selection gene (column 11, first full paragraph).

The rejection is improper, because the '556 does not teach each and every element of the claim. For example, the '556 patent does not disclose obtaining *PBMCs* from a patient immunized with a cancer antigen and stimulating the *PBMCs* with the cancer antigen in vitro, as required by the claim. According to the Office Action, CTLs and TILs are lymphocytes of PBMCs, such that the teachings of the '556 patent relating to the isolation of TILs and CTLs from patients do, in fact, anticipate obtaining PBMCs.

As stated in the Declaration of Dr. Ke Liu, TILs, which are T cells that are located in tumors, are not considered as lymphocytes of PBMCs, which by definition are a mixed population of white blood cells found in peripheral blood. The differences between TILs and PBMCs are also evident from the ways in which the ordinarily skilled artisan obtains these types of cells. Specifically, according to the Declaration of Dr. Ke Liu, the methodology used to isolate TILs from a patient involves an invasive surgical procedure on the patient, whereas the methods used to obtain PBMCs from a patient involve a simple blood draw or leukapheresis of the patient. In view of the foregoing, a teaching of the isolation of TILs does not anticipate obtaining PBMCs.

Further, with regard to CTLs, the act of stimulating CTLs is different from the act of stimulating PBMCs. As stated in the Declaration of Dr. Ke Liu, PBMCs are by definition a mixed population of white blood cells, including, for example, $CD8^+$ T cells, $CD4^+$ T cells, B cells, and natural killer cells, found in the peripheral blood. One of ordinary skill in the art recognizes that stimulating *just* CTLs, which are $CD8^+$ T cells, is different from stimulating PBMCs, since one would not be stimulating a mixture of different types of white blood cells; one would not be stimulating the other types of white blood cells of PBMCs, e.g., $CD4^+$ T cells, B cells and natural killer cells.

In view of the foregoing, the '556 patent does not teach each and every limitation of claim 1. Therefore, the '556 patent does not anticipate claim 1. Applicants accordingly request the withdrawal of the rejection.

Discussion of the Obviousness Rejections

Claims 1-3 and 5-13 are finally rejected as allegedly unpatentable in view of the '556 patent in view of one or more of the following secondary references: the '347 patent, Wang et al., the '957 patent, Roifman et al., Hattori et al., and Asami et al. The rejections are traversed for the reasons set forth below.

The rejections under Section 103 are improper, because the combinations of references do not teach or suggest all of the limitations of the rejected claims. Each of these rejections relies of the '556 patent as the primary reference, which reference allegedly teaches (i) obtaining PBMCs from a patient immunized with a cancer antigen and (ii) stimulating the PBMCs with the antigen of the cancer in vitro. However, as stated above, the '556 patent does not teach these features, since TILs are not lymphocytes of PBMCs, obtaining TILs is different from obtaining PBMCs, and stimulating CTLs is different from stimulating PBMCs.

In view of the foregoing, the primary reference of each rejection under Section 103 (a) (the '556 patent) does not teach the features of (i) and (ii) of claim 1. None of the secondary references cure the deficiencies of the '556 patent. Accordingly, the rejections under Section 103 cannot stand.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the

prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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